Received: 12 September 2022 | Revised: 23 November 2022 | Accepted: 3 January 2023

DOI: 10.1111/pai.13913

ORIGINAL ARTICLE

WILEY

Limited role of children in transmission of SARS-CoV-2 virus in households—Immunological analysis of 26 familial clusters

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Funding information
Medical Scientific Fund of the Mayor of the City of Vienna, Grant/Award Number: Covid003, Covid028 and 21205

Editor: Jon Genuneit

Abstract

Background: The impact of children on the transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remains uncertain. This study provides an insight into distinct patterns of SARS-CoV-2 household transmission in case of pediatric and adult index cases as well as age-dependent susceptibility to SARS-CoV-2 infection.

Methods: Immune analysis, medical interviewing, and contact tracing of 26 families with confirmed SARS-CoV-2 infection cases have been conducted. Blood samples were analyzed serologically with the use of a SARS-CoV-2-specific IgG assay and virus neutralization test (VNT). Uni- and multivariable linear regression and mixed effect logistic regression models were used to describe potential risk factors for higher contagiousness and susceptibility to SARS-CoV-2 infection.

Results: SARS-CoV-2 infection could be confirmed in 67 of 124 family members. Fourteen children and 11 adults could be defined as index cases in their households. Forty of 82 exposed family members were defined as secondarily infected. The mean secondary attack rate in households was 0.48 and was significantly higher in households with adult than with pediatric index cases (0.85 vs 0.19; $p < 0.0001$). The age (grouped into child and adult) of index case, severity of disease, and occurrence of lower respiratory symptoms in index cases were significantly associated with secondary transmission rates in households. Children seem to be equally susceptible to acquire a SARS-CoV-2 infection as adults, but they suffer milder courses of the disease or remain asymptomatic.

Conclusion: SARS-CoV-2 transmission from infected children to other household members occurred rarely in the first wave of the pandemic, despite close physical contact and the lack of hygienic measures.

Abbreviations: Ab, antibody; COVID-19, Coronavirus disease 2019; ELISA, Enzyme-linked immunosorbent assay; IC, index case; IgG, Immunoglobulin G; IU/ml, international units per milliliter; SAR, secondary attack rate; SARS-CoV-2, severe acute respiratory syndrome coronavirus type 2; U/ml, units per milliliter; VNT, virus neutralization test.

KEYWORDS
child, contagiousness, COVID-19, household transmission, SARS-CoV-2, secondary attack rate, susceptibility

1 | INTRODUCTION

Children contribute strongly to the spread of respiratory viruses, such as seasonal influenza or rhinoviruses[1] and therefore were considered as potential silent spreaders of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at the beginning of the pandemic. This assumption led to preventive measures such as school closures and isolation for a large number of children, which have had a significant impact on children's physical and mental health as well as their education. The evidence addressing the transmission of SARS-CoV-2 from infected children is still scarce, and the findings are controversial, with some studies suggesting children to be relevant spreaders of the virus[2–7] and others emphasizing their limited role in disease transmission.[8–18] Only few studies give direct evidence of children acting as index cases in their households.[19] While this could be underestimated due to asymptomatic courses of disease in children and in consequence less frequent testing, there is growing evidence that secondary attack rates from infected children are lower than from infected adults.

This study describes age-dependent SARS-CoV-2 transmission patterns within households and determines the potential role of children in this process. Additionally, we tried to define risk factors for higher contagiousness of index cases and higher susceptibility of exposed individuals. A better understanding of these issues is relevant not only for the control of future SARS-CoV-2 outbreaks but also to maintain the function of child-care facilities during the ongoing pandemic.

Key Message

Child-to-child and child-to-adult transmissions of SARS-CoV-2 were infrequent at the beginning of the pandemic, despite close physical contact and the lack of protective measures. Age of the index case, type of symptoms, and disease severity seem to play a role in the household transmission of SARS-CoV-2. Susceptibility of children to acquire SARS-CoV-2 infection seems to be similar to the susceptibility of adult individuals; however, children suffer from milder courses of the disease or remain asymptomatic.

2 | METHODS

2.1 | Study population

Twenty-six SARS-CoV-2 seropositive and two qPCR-positive children were defined in a cross-sectional study with 2069 schoolchildren in Austria, performed from May 2020 to July 2020 at the end of the first national lockdown.[20] These children, their parents, and siblings were invited to participate in a longitudinal, follow-up study, which aimed to describe the transmission patterns of SARS-CoV-2 infections in households (current manuscript) and to describe the immune response to SARS-CoV-2 and its longevity in time[21] (IRB of Medical University of Vienna #2104/2020). In total, 26 families with 124 family members were analyzed (Figure 1.). All subjects and/or legal representatives signed an informed consent form.

2.2 | Study design

This manuscript includes data from the first follow-up visit of a longitudinal study and gathers nearly all family members of families with identified SARS-CoV-2 infections (Figure S1). A comprehensive medical interview covering sociodemographic data, concomitant diseases, personal history of SARS-CoV-2 infection, and history of previous SARS-CoV-2 testing as well as detailed contact tracing was performed.

The blood samples were analyzed with the use of SARS-CoV-2-specific IgG against RBD (ELISA, Beijing Wantai Biological Pharmacy Enterprise, China) and virus neutralization test (VNT), as described previously.[22] For the ELISA, a cutoff of 1 U/ml (equivalent to 5.4 IU/ml) was used for detection of binding antibodies, for virus neutralization test (VNT), a titer of ≥10 was considered positive for the detection of neutralizing antibodies. Sample collection was performed during Nov–Dec 2020, which was around 9-month postsymptom onset, as assessed for symptomatic individuals.

2.3 | Study definitions

A confirmed SARS-CoV-2 infection was defined as having a positive SARS-CoV-2-specific IgG ELISA result in the study or a history of a positive qPCR test or a positive validated antibody testing.

The index case in a family was defined based on the chronology of the onset of the symptoms among confirmed SARS-CoV-2 cases. Defined index cases were categorized as child (0–18 years old) or adult (> 18 years old). Asymptomatic cases were considered as index cases only if they were the exclusive person tested seropositive in the household. Secondary cases were defined as further household members with a confirmed SARS-CoV-2 infection.

Symptomatic patients were defined as those who presented COVID-19-like symptoms in the period (±15 days) linked to a confirmed SARS-CoV-2 infection in the household.

Symptoms were categorized as upper respiratory, lower respiratory, neurologic, gastrointestinal, cardiovascular, joint and muscular symptoms, skin manifestation, fever, and nonspecific symptoms (such as tiredness and headache). Disease severity was defined as

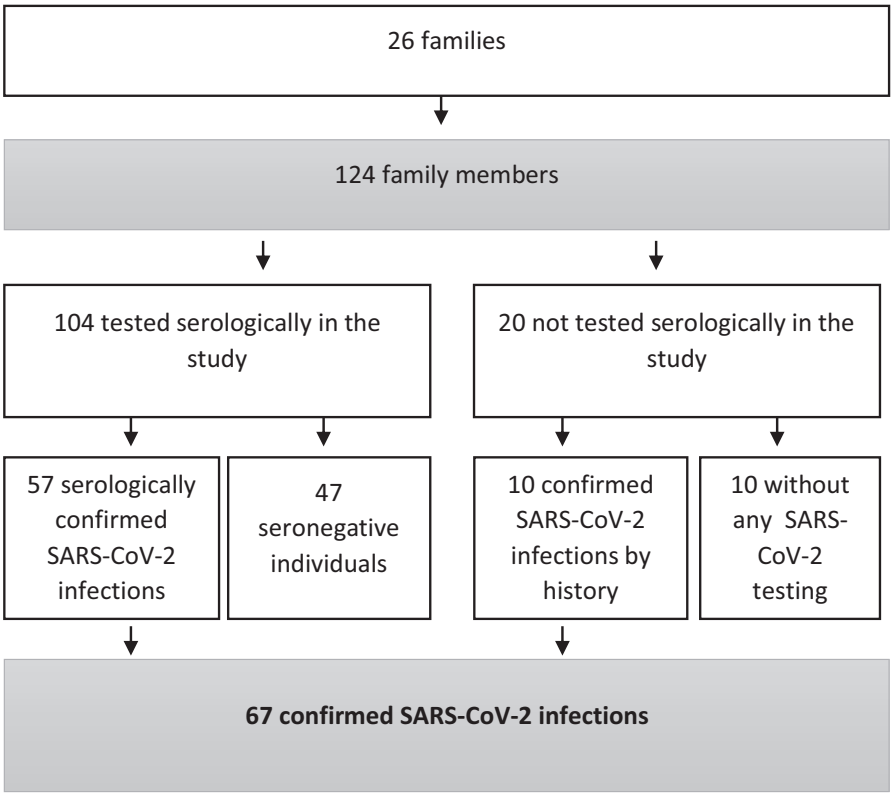

FIGURE 1 Overview of the study population.

minimal in case of exclusively unspecific symptoms lasting for a couple of days only; mild in case of mild symptoms with good general condition; intermittent in case of symptoms with a bad general condition, which could be managed in the outpatient settings; severe in case of a need for hospitalization and oxygen support.

The secondary attack rate (SAR) was defined as a rate of secondary infection among all contacts of the index case within the family and was based on a seropositive immune status of tested individuals or PCR positivity by history. Secondary attack rate was calculated for each family by dividing the number of confirmed SARS-CoV-2 infections among household contacts by the total number of tested household contacts.

Exposed individuals were defined as close, unprotected household contacts of defined index cases.

2.4 | Statistical analysis

Statistical analysis were performed in order to determine predictors for the SAR within the family and for the risk of secondary infection for each individual, defined as binary variable. To examine the association between the SAR and possible predictors, at first, univariable linear regressions were computed. Subsequently, a multivariable linear regression was performed, including all variables that were significant in the univariable models as predictors. Investigated predictors were sex, age (grouped into child or adult, cutoff 18 years), and occurrence of different symptoms in the index case (symptoms were categorized as described in the section Study definitions), as well as disease severity and duration of symptoms in the index case, number of people in the household and living space area.

The association between the risk of individual secondary infection (binary outcome—yes or no) and possible predictors (see below) was investigated using generalized linear mixed models with a link function (i.e., mixed effects logistic regression), including the random factor "family ID" in order to account for possible correlation within the family. In more detail, at first, univariable models were computed, followed by a multivariable mixed effects logistic regression model including all predictors that were significant in the univariable models as fixed effects and the "family ID" as a random effect. Predictors considered as independent variables in the univariable models were sex, age group (child vs. adult, cutoff 18 years), and comorbidities of the individual, living space area, number of people in the household, as well as age group (child vs. adult, cutoff 18 years), duration and type of symptoms (as described in section Study definition) of the index case.

Due to the exploratory character of the study, no correction for multiplicity was performed, and p-values <0.05 were considered statistically significant. All statistical analyses and graphs were generated in R (version 4.1.3), using packages stats (version 4.1.3), lme4 (version 1.1.30), and ggplot2 (version 3.3.6).

3 | RESULTS

3.1 | Demographic description of the study population

Twenty-six families agreed to participate. In total, 124 family members were analyzed, 62 children (5–18 years old) and 62 adults (>18 years old). One hundred four individuals provided a full medical

history and a blood sample for serological analysis, 52 children and 52 adults (Table S1). In addition, for 20 family members, who did not provide blood samples in the study, medical history of COVID-19-like symptoms and/or qPCR- and/or antibody testing could be evaluated. The size of families varied from three to seven members (Table S2).

3.2 | Confirmation of SARS-CoV-2 infection

In total, 57 of 104 (54.8%) subjects tested positive for the SARS-CoV-2-specific IgG ELISA (Wantai) Neutralizing antibodies in VNT were detected in 39 of 57 (68.4%) seropositive subjects. The titers of SARS-CoV-2-specific IgG and VNT did not differ significantly between seropositive children and adults. Additionally, 10 family members, not tested in the study, reported a history of a positive SARS-CoV-2 testing (Table 1.).

3.3 | Clinical presentation of SARS-CoV-2 infections

Among 57 seropositive individuals, 46 (80.7%) were symptomatic: 23 of 31 (74.2%) children and 23 of 26 (88.5%) adults. General symptoms, such as headache and tiredness, were most frequently reported, regardless of age, followed by lower respiratory symptoms in adults, taste and smell disorders and upper respiratory symptoms in children. There were no severe courses, cases of hospitalization, or deaths in any age group. The majority of symptoms were reported for March–April 2020. In general, adults reported more symptoms than children and the duration of these was longer (Table S3).

3.4 | Contact tracing

Contact tracing revealed 25 household index cases and their exposed household contacts. In case of one family, the determination of the index case in the household was inconclusive, and therefore was not analyzed for transmission patterns. Four family members could be defined as "not exposed" to SARS-CoV-2 in the household, due to travel activities coinciding with SARS-CoV-2 infection of the index case, and therefore were also not analyzed. Thus, 25 families with 107 family members were analyzed for age-dependent household virus transmission patterns, and 82 exposed contacts were analyzed for age-dependent susceptibility patterns (Figure 2.).

3.5 | Age-dependent transmission pattern

Fourteen children (Figure 3I) were defined as index cases in their families. The majority of them could be linked to SARS-CoV-2 infections in educational settings. These pediatric index cases reported mild or minimal COVID-19-like symptoms, and only two of them were asymptomatic. In total, 10 of 46 (21.7%) contact persons of these pediatric index cases could be defined as secondary infected.

Eleven adults (Figure 3II) were defined as index cases in their family, and the infection could be assigned either to an occupational transmission, traveling, or contact with the healthcare system. These individuals reported mild or intermittent COVID-19-like symptoms, and none of them were asymptomatic. In total, 30 of 36 (83.3%) contact persons of these adult index cases could be defined as secondary infected.

3.6 | Secondary attack rate and the risk factors for higher contagiousness

Overall, the SAR for all exposed individuals was estimated at 0.48. Secondary attack rate was significantly lower ($p < 0.0001$) in households with pediatric index cases than households with adult index cases (0.19; 0.85; respectively) (Figure 4A).

The age group of index cases ($p < 0.001$), severity of disease ($p < 0.001$), and occurrence of lower respiratory symptoms ($p < 0.05$) were found to be associated with higher SARs in households in univariable analyses. In the subsequent multivariable analysis, solely the age group of the index cases remained statistically significant (Tables 2 and S4).

3.7 | Susceptibility to acquire SARS-CoV-2 infection and its risk factors

In total, 82 tested family contacts of 25 defined index cases were analyzed. Twenty-four of 46 (52.2%) adult contacts and 16 of 36 (44.4%) pediatric contacts tested positive. Children were not found to be less susceptible to acquire SARS-CoV-2 infection than adults (Table 2; Figure 4B). Mixed effect logistic models showed no statistically significant associations between age groups, sex, or underlying comorbidities of exposed individuals and the risk of acquiring infection. The age group of index case (child vs. adult, $p < 0.001$), with whom an exposed individual was in contact with, and the occurrence of lower respiratory symptoms ($p < 0.05$) in the index case were statistically significant in the univariable analyses. In the multivariable model, only the age group of the index case remained significantly associated with the risk of acquiring infection ($p < 0.001$) (Table S5).

4 | DISCUSSION

Up to date, evidence of children acting as the source of SARS-CoV-2 infection is scarce. In a recently published cross-sectional seroprevalence study on schoolchildren, we were able to define a group of children infected in school settings and another group infected secondarily to their parents.[20] The comprehensive analysis of these children and almost all their family members provided a unique insight into distinct age-dependent patterns of transmission in households

TABLE 1 Confirmation of SARS-CoV-2 infection among analyzed family members.

	Total	Children (≤18 years old)	Adults (>18 years old)
Individuals tested in the study (n)	104	52	52
Individuals with SARS-CoV-2 antibodies detected in the study	57/104 (54.8%)	31/52 (59.6%)	26/52 (50.0%)
Antibody levels (IU/ml), mean	50.06	52.71	44.75
Individuals with SARS-CoV-2 neutralizing antibodies detected in the study	45/104 (43.7%)	25/52 (48.1%)	14/52 (26.9%)
VNT -Titer (ranges)	<1:10 – ≥1:80	<1:10 – ≥1:80	<1:10 – ≥1:80
Positive qPCR by history	10/104 (9.6%)	5/52 (9.6%)	5/52 (9.6%)
Positive antibody testing by history	17/104 (16.3%)	0/52 (0.0%)	17/52 (32.7%)
COVID-19-like symptoms	59/104 (56.7%)	29/52 (55.8%)	30/52 (57.7%)
Other family members not tested in the study (n)	20	10	10
Positive qPCR test by history	9/20 (451.0%)	0/10 (0.0%)	9/10 (90.0%)
Positive antibody testing by history	1/20 (5.0%)	0/10 (0.0%)	1/10 (10.0%)
COVID-19-like symptoms	9/20 (45.0%)	0/10 (0.0%)	9/10 (90.0%)

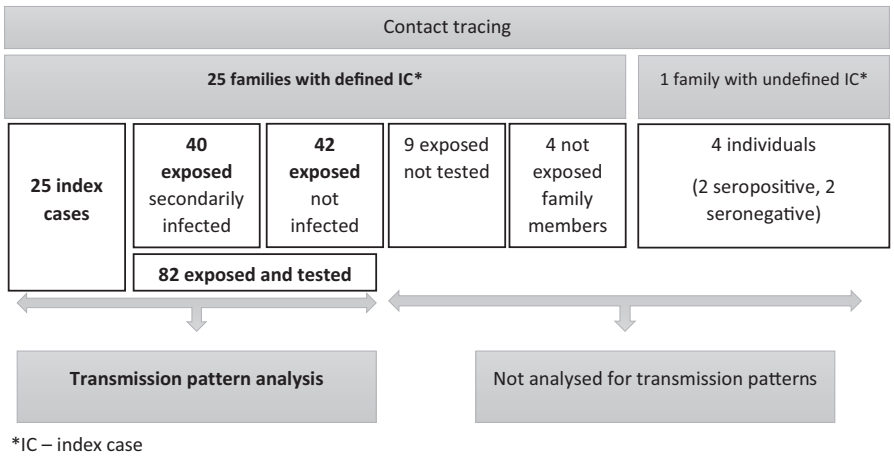

FIGURE 2 Overview of contact tracing.

at the beginning of pandemic. Our data suggest that children may acquire SARS-CoV-2 and act as a source of infection in households, but the transmission of the virus to other family members occurs infrequently.

The overall SAR of SARS-CoV-2 in households was estimated at 48%, and differed significantly between households with children and adults acting as a source of SARS-CoV-2 infection. Our observation suggests that children may be less contagious than adults. Only the age of index cases, severity of the disease, and occurrence of lower respiratory symptoms seem to be risk factors associated with higher contagiousness.

This observation, although based on a small study group, strengthens the data on a limited role of children in the SARS-CoV-2 transmission compared with adults. Many recent studies suggest lower risk of transmission of SARS-CoV-2 infection from infected children in both household[8–13,23] and educational settings.[14–16,18,24] In addition, most countries did not observe any significant increase in SARS-CoV-2 infections after school reopening, with the exception of Israel, where school opening coincided with the opening of other facilities. However, contradictory data on higher or equal infectivity of children in respect to adults have been published as well.[2–7]

In fact, epidemiological data on the contagiousness of children need to be analyzed with caution. Many transmission studies have a retrospective character and are based on a history of symptoms or a history of positive PCR, and only a few have performed comprehensive immunological testing of all contacts. Thus, children may be underrepresented due to the lack of or very mild symptoms and consequently less frequently or later performed PCR testing. The possibility of false-negative PCR testing in asymptomatic individuals needs to be acknowledged as well.

Furthermore, the risk of secondary infection is not only a matter of contagiousness of the index case but also a matter of susceptibility of the exposed individual, which seems to be overseen in many transmission studies. Many studies suggested lower susceptibility of acquiring SARS-CoV-2 infection by children.[25–30] This trend cannot be observed in our study. Only the age of the index case but not the age of the exposed individual itself was linked to a higher risk of

	I														II											III
family ID	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18	F19	F20	F21	F22	F23	F24	F25	F26
index case in the family	C	C	C	C	C	C	C	C	C	C	C	C	C	C	A	A	A	A	A	A	A	A	A	A	A	UNK
family members	A	A	A	A	A	A	A	A	A	A	A	A	C	A	A	A	A	A	A	A	A	A	A	A	A	A
	A	A	A	A	A	A	A	A	A	A	A	C	C	A	C	C	C	C	C	C	C	C	C	C	C	C
	C	C		C	C	A	C	C	C	C		A	A	C	C	C	A		C	C	C	A	A	C	C	A
				C	C	C		C	C				A		C	C	A		C	C	A				A	A
					C				A				C		A		C		C		C					
									C						C				C							
secondary attack rate	0,5	0	0	0	0,2	0,33	0,33	0	0,2	0	0	0	0,8	0,33	1	0,67	1	1	0,5	0,75	1	1	1	0,67	0,75	NA

confirmed SARS-CoV-2 infection (seropositive in the study/qPCR positive by history)
seronegative in the study
seronegative in the study (not exposed)
did not provide blood sample for the study
did not provide blood sample for the study (not exposed)
A adult
C child

FIGURE 3 Patterns of SARS-CoV-2 infection in 26 households grouped by the age of index case. Each column represents a family with an ID (F1 to F26) . The families are grouped according to the age of index cases: families with (I) pediatric index cases and (II) adult index cases in the household. In case of family F26 (III), index case could not be identified. Each color -fulfilled cell represents a family member (green: SARS-CoV-2 seronegative individual; red: SARS-CoV-2 seropositive or PCR+ individual; gray: not tested family member). A, adult (>18 years old); C, children (5–18 years old).

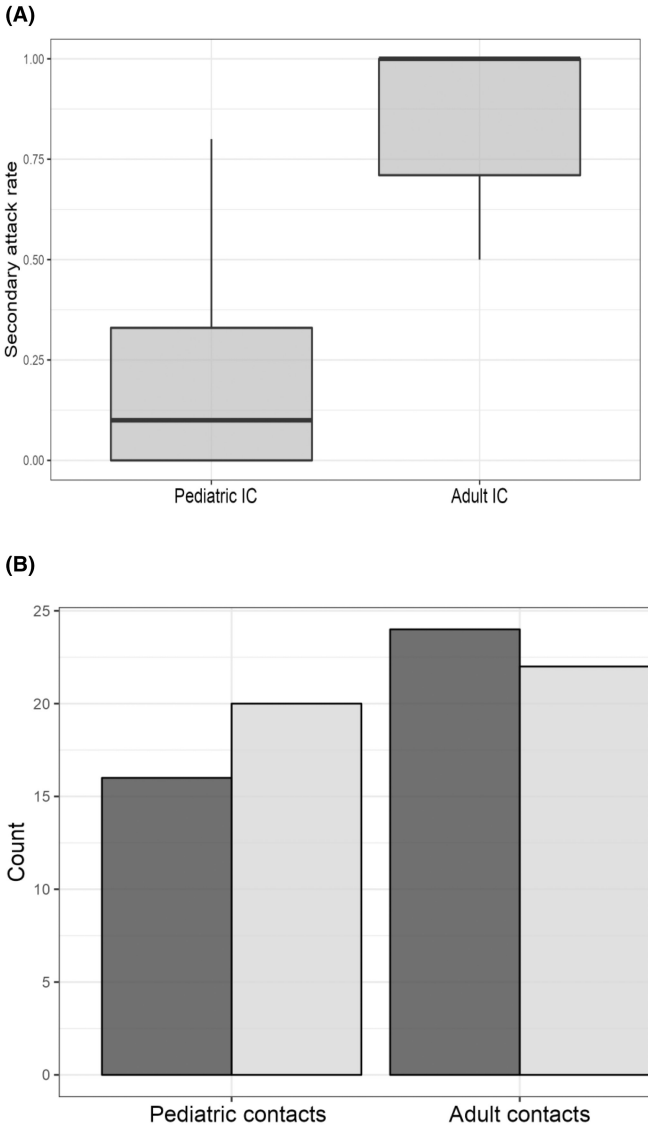

FIGURE 4 Age-dependent SARS-CoV-2 contagiousness and susceptibility. (A) Age-dependent SARS-CoV-2 contagiousness of index cases. Boxplots for the secondary attack rate categorized by the age group of the index case (pediatric vs adult index case). (B) Age-dependent SARS-CoV-2 susceptibility of exposed individuals. Bar charts showing the counts of secondary infections categorized by the age group of the exposed individuals (pediatric vs adult contacts).

TABLE 2 Contagiousness of index cases and susceptibility of exposed contacts by age.

	In Total	Pediatric Index case	Adult Index Case
Number of families	25	14	11
Sex ratio of index cases F:M	10:15	6:8	4:7
Age of index case (years, mean)	29.6	13.5	50.0
IC symptomatic (n)	23	12/14	11/11
Severity of the disease in index cases			
No symptoms	2	2/14 (14.3%)	0/11 (0.0%)
Minimal symptoms	3	3/14 (21.4%)	0/11 (0.0%)
Mild symptoms	14	9/14 (64.3%)	5/11 (45.5%)
Intermittent symptoms	6	0/14 (0.0%)	6/11 (54.5%)
Type of symptoms in index cases			
Fever (n)	13	5/14 (35.7%)	8/11 (72.7%)
Upper resp. symptoms (n)	12	5/14 (35.7%)	5/11 (45.5%)
Lower resp. symptoms (n)	12	3/14 (21.4%)	9/11 (81.8%)
Gastrointestinal symptoms (n)	5	3/14 (21.4%)	2/11 (18.2%)
Anosmia/ageusia (n)	11	6/14 (42.9%)	5/11 (45.5%)
Symptomatic days (mean)	8.5	5.0	12.9
Titres of IC (mean)			
IC - SARS-CoV-2-spec. IgG (IU/ml)	50.06	52.71	44.75
Occurrence of secondary infection in households			
Families with secondary infection	18/25 (72.0%)	7/14 (50.0%)	11/11 (100%)
Secondary SARS-CoV-2 infections in exposed contacts			
Number of exposed contacts	82	46	36
Number of secondary SARS-CoV-2 infections among exposed contacts	40/82 (48.8%)	10/46 (21.7%)	30/36 (83.3%)
Secondary SARS-CoV-2 infections in exposed pediatric contacts			
Number of exposed pediatric contacts	36	17	19
Number of pediatric secondary infections among pediatric exposed contact	16/36 (44.4%)	2/17 (11.8%)	14/19 (73.7%)
Secondary SARS-CoV-2 infections in exposed adult contacts			
Number of exposed adult contacts	46	29	17
Number of adult secondary infections among adult exposed contacts	24/46 (52.2%)	8/29 (27.6%)	16/17 (94.1%)
Confounders			
Living area, m^2 (mean)	122.2	124.4	119.4
Number of people in Household (mean)	4.64	4.43	4.91
Living area p. person, m^2 (mean)	35.72	28.45	44.9

acquiring SARS-CoV-2 infection in logistic mixed models. The reason for this divergence could be a prospective character of our study and similar proportion of pediatric and adult tested individuals, as well as the fact of serological testing, which revealed asymptomatic/mildly symptomatic individuals as well.

It has been suggested that children acquire COVID-19 mostly at home or through contact with other family members.[19,26,31] Our study showed a similar proportion of households with pediatric and adult index cases. The distinctness of our findings can be caused, apart from different population selections, by a different time point of the study assessment. Most of the abovementioned studies were conducted during a time when schools were closed and physical distancing was implemented. Under these circumstances, children's social contact with others than their household was limited. In contrary to that, most COVID-19 infections in our study can be linked to March–April 2020, when schools were still open and no hygienic measures, such as wearing a facemask or social distancing, were implemented yet.

Some limitations of our study need to be addressed. Although we tested all individuals regardless of symptoms and found

only 13asymptomatic infections, defining index cases based on the chronology of symptoms is still exposed to inaccuracies. Asymptomatic individuals might be underrepresented as index cases. Additionally, tertiary transmission within the household is impossible to define. In consequence, all subsequent cases are classified as secondary to the index case. Finally, seropositivity of secondary cases could potentially be caused by a later SARS-CoV-2 infection, not related to the confirmed infection in the household. This, however, was verified by clinical data and did not reveal any hint of later SARS-CoV-2 infections.

The small sample size does not allow any definitive conclusions on population basis; however, it provides detailed insights into household transmission. Serological testing of almost all family members combined with the history of PCR testing, detailed medical history, and contact tracing assures the possibility of a comprehensive analysis of transmission patterns in households.

Similar proportion of pediatric and adult index cases provides a unique opportunity for a comparison of age-dependent transmission patterns, which cannot be done in big studies including only a small proportion of pediatric index cases.

Although the data from an early stage of the pandemic may not mirror transmissibility in case of new variants of the virus, it provides an opportunity to analyze the patterns of transmission in settings of "normal life."

In conclusion, our study shows that children can acquire a SARS-CoV-2 infection in educational settings and at home. In most cases, the infection could be linked to adult index cases infecting the child, rather than a child-to-child transmission. Infected children did not seem to be very contagious to their parents and siblings, despite the close physical contact in the household. In fact, our infected children did not apply any isolation precautions with respect to their relatives during symptom occurrence. The possible explanation for that could be: (a) rapid virus neutralization in children and consequently lower virus load, (b) mild or minimal symptoms, or (c) occurrence of symptoms with reduced risk of droplet transmissions.

This observation, if confirmed in large prospective studies and with new virus variants, could significantly influence COVID-19 policies in child-care facilities and spare children from unnecessary isolation during the ongoing pandemic.

AUTHOR CONTRIBUTIONS

JS was involved in conceptualization, data curation, formal analysis, investigation, methodology, project administration, visualization, writing—original draft, and writing—review & editing. KSch and SK were involved in conceptualization, data curation, investigation, methodology, project administration, and writing—review & editing. JH, AS, and VD were involved in data curation, investigation, and writing—review & editing; LW and KS were involved in investigation, methodology, validation, and writing—review & editing; AG and PK were involved in formal analysis, methodology, software, and writing—review & editing; FG and TF were involved in formal analysis, and writing—review & editing; ZS was involved in conceptualization, formal analysis, funding acquisition, methodology, project administration, resources, supervision, validation, and writing—review & editing.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/pai.13913.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Sieber J, Schmidthaler K, Kopanja S, et al. Limited role of children in transmission of SARS-CoV-2 virus in households—Immunological analysis of 26 familial clusters. *Pediatr Allergy Immunol*. 2023;34:e13913. doi:10.1111/pai.13913